Chronicle EP, Mulleners WM. Anticonvulsant drugs for migraine prophylaxis. Cochrane Database of Systematic Reviews 2004, Issue 3, Art # CD003226.

Design: Meta-analysis of clinical trials

PICOS:
- Patient population: adults with headache diagnoses meeting criteria for migraine, based on at least some distinctive features of migraine (nausea/vomiting, unilateral pain, severe pain, throbbing character, phono/photophobia, aura)
- Interventions: A commercially available anticonvulsant drug in at least one arm of the study
  o The list of eligible anticonvulsant drugs was extensive, with 33 drugs included in the search
  o The drugs actually analyzed were sodium valproate, divalproex sodium, gabapentin, carbamazepine, and topiramate
- Comparison: Placebo, no intervention, treatment with other drugs, or different doses of the same drug
- Outcomes: most analyses were either on headache frequency (per 28 days) or on migraine "responders," considered to be the proportion of patients with a 50% reduction in headache frequency or on the headache index (defined as a function of frequency, intensity, and duration)
- Study types: Randomized or pseudo-randomized (allocation based on a non-random process unrelated to treatment selection or expected response)

Study type and selection:
- Databases included Cochrane Pain Trials Register, PubMed, and EMBASE
- Additional searches were done on the reference lists of review articles and selected clinical trials
- Two headache journals, Headache and Cephalalgia, were hand-searched in their entirety through April 2006
- Methodologic quality was assessed with a 5 point scale, based on randomization, adequacy of description of method of randomization, double blinding, adequacy of description of double blinding, and description of withdrawals and dropouts

Pertinent results:
- 23 trials were included in the review, of which 19 compared various anticonvulsants with placebo:
  o 6 trials of topiramate
  o 4 trials of divalproex sodium
  o 2 trials of sodium valproate
  o 2 trials of gabapentin
  o 1 trial each of acetazolamide, carbamazepine, clonazepam, lamotrigine, and vigabatrin

- Anticonvulsants as a class reduced headache frequency, but there was heterogeneity in the findings of the combined analysis
  - In 2 studies of sodium valproate with 126 participants, the frequency of migraine was .087 standard deviations (SD) in the valproate patient compared to placebo (0.8 SD or more is considered a large effect size)
  - In 4 studies of topiramate, the effect size was 0.37 SD (a small to moderate effect size)
- Anticonvulsants as a class also increased the proportion of patients with a 50% reduction in migraine "responders;" patients taking anticonvulsants were 2.3 times as likely to be responders as were patients taking placebo; again, there was heterogeneity between studies of various drugs
  - In 4 trials of divalproex sodium with 574 patients, the odds of being a responder were 3.34 times as great for valproate patients over placebo patients; however, the largest of the 4 studies reported no difference between valproate and placebo, generating significant heterogeneity between studies
  - In 6 trials of topiramate with 898 patients, the odds of being a responder were also 3.34 in favor of topiramate; in contrast to divalproex sodium, the results were not significantly heterogeneous, and only the smallest trial failed to report a significant difference between topiramate and placebo
- Notable adverse effects included nausea for valproate and paresthesia for topiramate
- Additional analyses, including those for gabapentin and for head-to-head comparisons between anticonvulsants versus other active drugs, were less conclusive
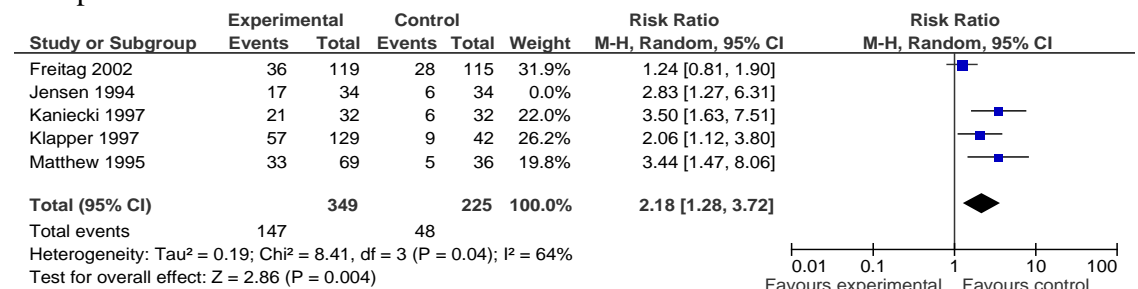
Authors' conclusions:
- Sodium valproate/divalproex sodium show generally consistent beneficial effects for migraine prophylaxis; however, because the drug is teratogenic, is should be prescribed cautiously in women who may become pregnant
- Topiramate shows generally consistent benefit for migraine prophylaxis also
- The analyses faced some difficulties in deriving adequate information from trials in which the reporting of results was often marginally adequate
- There was not sufficient information to judge the effectiveness of anticonvulsants in alleviating the associated symptoms of migraine, such as nausea and aura
- Because of the lack of a validated case definition, the results cannot be extrapolated to chronic migraine, transformed migraine, or chronic daily headache

Comments:
- The authors' dismissal of chronic migraine (CM) from the analysis is based in part on the difficulties in the case definition of CM, due to controversies surrounding the practicality of the case definition of medication overuse headache, from which CM needs to be distinguished (Olesen 2006); the

guideline implications of this controversy should not affect the interpretation of the results of the meta-analysis

- Although not reported for "responders" to valproate and topiramate, the relative risks for both drugs can be calculated and are lower than the reported odds ratios of 3.34 for both drugs; for divalproex sodium, the RR is 2.18, and for topiramate, the RR is 2.17
- Although the analyses did not combine the 4 studies of divalproex sodium and the 1 study of sodium valproate, the similarity of the pharmacology justifies combining all 5 studies; the pooled RR is 2.26 in favor of treatment over placebo:

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Freitag 2002	36	119	28	115	31.9%	1.24 [0.81, 1.90]
Jensen 1994	17	34	6	34	0.0%	2.83 [1.27, 6.31]
Kaniecki 1997	21	32	6	32	22.0%	3.50 [1.63, 7.51]
Klapper 1997	57	129	9	42	26.2%	2.06 [1.12, 3.80]
Matthew 1995	33	69	5	36	19.8%	3.44 [1.47, 8.06]
Total (95% CI)		349		225	100.0%	2.18 [1.28, 3.72]
Total events	147		48			

Heterogeneity: Tau² = 0.19; Chi² = 8.41, df = 3 (P = 0.04); I² = 64%
Test for overall effect: Z = 2.86 (P = 0.004)

Favours experimental | Favours control (0.01 0.1 1 10 100)

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- Because most of the differences between the preparations of valproic acid relate to pharmacodynamic variables, and because the response to treatment is dependent on what occurs in the steady state, combining the results in this fashion appears reasonable
- Because the results for topiramate are more homogeneous than for valproate, topiramate warrants a stronger evidence statement than valproate

Assessment: High quality meta-analysis supporting good evidence that valproate is more effective than placebo in reducing the frequency of migraine headache, and strong evidence that topiramate is similarly effective

Reference:
Oelsen J, Bousser M-G, et al. New Appendix Criteria Open for a Broader Concept of Chronic Migraine Cephalalgia 2006; 26:742-746.